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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/509,239	03/23/00	BRUCK C	B45110

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EXAMINER	
WINKLER,U	
ART UNIT	**PAPER NUMBER**
1648	9

DATE MAILED: 02/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/509,239	BRUCK ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-77* is/are pending in the application.

4a) Of the above claim(s) *55-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Applicant's election of Group III in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

Applicant is required to update the status (pending, allowed, ect.) of all parent priority applications in the first line of the specification.

Sequence listing

Applicant's CRF and paper sequence listing have been entered.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 1, is attached to the instant Office action.

Drawings

The drawings are objected to, please see Notice of Draftsperson's Review attached to the instant Office Action. Correction is required.

Claim Objections

Claim 32 is objected to because of the following informalities: The claim is directed at non-elected subject matter, specifically (a) a Tat fusion protein and (b) a Nef fusion protein. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant invention is drawn to a vaccine composition comprising a Tat-Nef fusion protein or Nef-Tat fusion protein. The specification does not sufficiently support the claimed vaccines. The term "vaccine" by definition implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members

of a community to reduce the number of carriers of a disease and to prevent others contracting the disease. The specification describes the elicitation of an immunoglobulin response to a Nef-Tat fusion protein in mice. There is insufficient evidence that such a study would correlate with *in vivo* efficacy in humans. It is well known in the art that retroviral therapies, especially HIV therapies, are refractory to anti-viral therapies (see Fahey et al., Clinical Experimental Immunology, 1992; Letvin, Science, 1998). The obstacles to developing a successful therapy of HIV are well documented in the literature. These obstacles include 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with the respect to the gene encoding the envelope protein. 2) The fact that the mode of viral transmission includes both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission. 3) The establishment of a latent viral infection. 4) The ability of the virus to evade the immune responses in the central nervous system due to the blood-brain barrier. 5) The complexity and variation of the pathology of HIV infection in different individuals. 6) The inability of a natural infection to one strain of HIV to protect an individual from being infected with another strain of HIV (Machuca et al. Intervirology 1998, see discussion). These obstacles establish that the contemporary knowledge in the art would not allow one of skill in the art to use the claimed vaccine to treat and/or prevent HIV infection without undue experimentation. Furthermore, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Applicants have not provided any convincing evidence that their claimed vaccine is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance in to allow one skilled

in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Claims 32, 36 and 50-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. While the specification describes actual Tat mutations, Lys 41→Ala, Arg 78→ Lys and Asp 80→Glu, the specification does not describe how these mutations effect the immunogenic character of Tat, let alone the Nef-Tat fusion protein. The specification does not provide a sufficient written description, for the ordinary artisan to predict what mutations are allowable or even desirable for eliciting an immune response. Therefore, the claimed mutated Tat or derivative thereof in the context of the fusion protein lacks written description in the instant specification.

Claims 32, 35 and 50-53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification does not provide a sufficient written description, for the ordinary artisan to predict what mutations are allowable or even desirable for eliciting an immune response. Therefore, the claimed mutated Nef or derivative thereof in the context of the fusion protein lacks written description in the instant specification.

Claims 32, 50-53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification does not provide a sufficient written description for the alternate orientations of the chimeric fusion protein. Therefore, the claimed mutated Nef or derivative thereof in the context of the fusion protein lacks written description in the instant specification.

Claims 32, 35, 36 and 50-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant invention is drawn to a fusion protein containing a mutated Nef or a mutated Tat or both in the context of a fusion protein; the orientation of the fusion protein can be Nef-Tat or Tat-Nef. The specification teaches the immunogenicity of a Nef-Tat fusion protein in which neither Nef or Tat is mutated (see figure 6A). However, it would not be possible to predict the efficiency of the production of an antibody response to a fusion protein containing a mutated Nef or Tat protein or both. It is well known in the art that when using synthetic amino acid sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is nor how immunogenic it is. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quartenary structure of a protein in a physiological situation. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties,

phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937, 1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Partidos et al. (Molecular Immunology 1992) teach that the orientation of chimeric peptide containing both B and T cell epitopes is important in the ability to induce antibodies (see abstract). Since the specification has not identified which amino acids provide the critical or essential characteristics of the fusion protein epitopes and the specification has not taught alternate orientations of Nef-Tat or Tat-Nef for eliciting a prophylactic antibody response, based on the specification or the art in general, the claimed invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear from the claim in what orientation the Nef, Tat and fusion partner are coupled together.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Pat. No. 5,962,635 Azad et al.

U.S. Pat. No. 5,221,610 Montagnier et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

Jeffrey Stucker

JEFFREY STUCKER
PRIMARY EXAMINER